GF23–Mediated Hypophosphatemia Impaired tubular reabsorption of phosphate is the underlying patho genesis of hypophosphatemia in many disorders. In 1937, Albright and coworkers reported their studies of a 16–year–old boy with longstanding rickets in whom standard doses of vitamin D failed to produce clinical improvement.68 Healing of the skeletal disease observed after administration of extremely high doses of vitamin D introduced the concept of “vitamin D resistance” in certain types of rickets. Subsequently, vitamin D–resistant rickets has been clas sified into several clinical and biochemical subtypes, the most com mon of which is XLH, characterized by elevated levels of FGF23 that result in renal phosphate wasting and inhibition of the vitamin D 1–alpha–hydroxylase, thus impairing production of 1,25(OH)2D.69 Affected individuals have hypophosphatemia, low renal resorption of phosphate, inappropriately normal 1,25(OH)2D levels (because hypophosphatemia normally increases 1,25(OH)2D), and modest elevations in serum PTH. Children usually present with clinical and radiographic evidence of rickets, growth retardation, and dental caries. In adults, the clinical course is often complicated by osteoarthritis and mineralization of the tendon–bone insertion sites (enthesopathy).22 XLH is traditionally treated with a combination oral phosphate and 1,25(OH)2D (calcitriol). More recently, a novel anti–FGF23 blocking antibody (burosumab) was approved for the treatment of children and adults with XLH. While antibody treatment is able to increase serum phosphate levels into the low normal range without increasing serum PTH levels,70 no therapy has been shown to normalize growth and skeletal mineralization.71,72 Positional cloning used to identify the molecular basis for XLH73 revealed a mutation in the PHEX gene, which is structurally similar to genes encoding a group of membrane–bound metalloendopeptidases.74 It is still unclear how the mutations in this gene lead to increased levels of FGF23. Autosomal dominant hypophosphatemic rickets (ADHR) is also characterized by isolated renal tubular phosphate wasting and inap propriately normal plasma 1,25(OH)2D levels. Positional cloning identified FGF23 as the gene mutated in ADHR.75 These mutations, localized to a subtilisin–like proprotein convertase cleavage site, decrease inactivation of FGF23, thereby leading to elevated circulating levels, which result in renal phosphate wasting. In contrast to XLH, ADHR displays variable and incomplete penetrance and may not present until adolescence/adulthood. Iron deficiency increases FGF23 mRNA expression; thus, iron deficiency can lead to hypophosphate mia in normal individuals and unmask ADHR.76 Treatment of iron deficiency in patients with ADHR has been shown to normalize serum FGF23 and phosphate levels.77 Two forms of autosomal recessive hypophosphatemic rick ets (ARHR) have been described. The genetic basis for ARHR1 is a mutation in dentin matrix protein 1 (DMP1), which, like FGF23, is expressed in osteocytes. The clinical features are similar to those seen in XLH, including hypophosphatemia, inappropriately normal or low 1,25–dihydroxyvitamin D, and high circulating FGF23.78 ARHR2 is secondary to mutations in ectonucleotide pyrophosphatase/phospho diesterase1 (ENPP1), which cleaves adenosine triphosphate to release the mineralization inhibitor PPi. Clinical characteristics are similar to ADHR1; however, FGF23 levels are not always elevated. Loss–of function mutations of ENPP1 are the molecular basis for generalized arterial calcification of infancy, an often fatal disorder.79 Mutations in FAM20c, a kinase that can phosphorylate FGF23, osteopontin and DMP1, have been associated with an FGF23–dependent hypophos phatemic syndrome characterized by dental abnormalities and ectopic mineralization.80 Dent and Gertner also described three patients with

fibrous dys plasia with hypophosphatemic osteomalacia or rickets.81 Subsequent investigations revealed that dysplastic tissue produces FGF23, impli cating this hormone in the pathogenesis of the renal phosphate leak.82 Treatment of these and other rare inherited disorders of phosphate homeostasis are discussed in Chapter 53. Tumor-induced osteomalacia is an acquired hypophosphatemic syndrome secondary to tumor secretion of phosphaturic factors, includ ing FGF23. In 1959, Prader and coworkers described the case of an 11-year-old girl who, over the course of a year, developed severe symp tomatic rickets accompanied by hypophosphatemia, renal phosphate wasting, and mild hypocalcemia.83 The child was found to have a large tumor that was pathologically diagnosed as a reparative giant cell granu loma of a rib. Following excision of the tumor, the rickets healed without any specific therapy. It was postulated that the tumor may have pro duced a "rachitogenic substance." Since that time, numerous patients have been described with tumor-induced osteomalacia. One review reported that, of 72 tumors, 40 were localized to bone and 31 to soft tis sues; two-thirds of the tumors occurred in the extremities.84 More than one-third of the tumors were classified as vascular tumors, and half of these were hemangiopericytomas. All of the tumors exhibited promi nent vascularity, multinucleated giant cells, and primitive stromal cells. Ten of the tumors were classified as malignant. Although most neo plasms associated with this syndrome are of mesenchymal origin, cases associated with prostate carcinoma and pheochromocytoma have been reported. In most of the reported cases, the removal of the tumor results in clinical cure of the osteomalacia or rickets; however, the tumors are usually small and often are not identified until years after development of clinical osteomalacia. Recurrence of the tumor or inadequate removal of the malignancy may prevent a complete clinical response. Patients with tumor-induced osteomalacia exhibit hypophospha temia, renal phosphate wasting, and normal serum calcium levels. Serum PTH levels are variable. Tumors that have been isolated express high levels of FGF23 mRNA,85 and many have a fibronectin:FGFR1 or fibronectin:FGF1 fusion thought to be pathogenic in the increased FGF23 production.86 Whereas other phosphaturic factors have been found in these tumors, normalization of circulating FGF23 is seen after removal of the tumor and correlates with resolution of the hypophos phatemia. As in XLH, inappropriately low levels of serum 1,25(OH)2D are observed owing to expression of FGF23,85 and tumor resection may result in a dramatic increase in 1,25(OH)2D, resulting in transient hypercalcemia. Tumors secreting phosphaturic factors may be small and in obscure locations, making tumor localization challenging. The 68Ga-DOTATATE positron emission tomography (PET)/computed tomography (CT) scan is the most sensitive and specific for localiza tion of these tumors.87 Other imaging modalities used include octreos can–single-photon emission CT/CT, (18F)-fluorodeoxyglucose–PET/ CT, and 3T magnetic resonance imaging (MRI). 87,88 If the tumor secrets a high amount FGF23, venous sampling may be used for tumor localization.88 If the tumor cannot be localized or resected, affected individuals, like those with hypophosphatemic rickets, are tradition ally treated with combination oral phosphate and calcitriol therapy. The phosphate in oral supplements binds serum calcium, resulting in a transient decrease in serum ionized calcium levels and rise in serum PTH levels.89 The calcium-sensing receptor agonist cinacalcet has been used to treat patients with tumor-induced osteomalacia or hypophos phatemic rickets as adjunctive therapy to improve hypophosphatemia and prevent hyperparathyroidism.89,90 The anti-FGF23 antibody has recently been approved as a

.therapy for tumor-induced osteomalacia but has not been shown to cure the osteomalacia